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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/591,263	07/11/2007	James Russell	RUSSELL6	9299

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EXAMINER	
SHAW, AMANDA MARIE	
ART UNIT	PAPER NUMBER
1634	
MAIL DATE	DELIVERY MODE
10/13/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,263	RUSSELL ET AL.	
	Examiner	Art Unit	
	AMANDA SHAW	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *1,2,4,10-14,16,18-20,22,23 and 32-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36, 44-47, 49, 58, 60-62, 64-65, 68, 88-89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/21/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1,2,4,10-14,16,18-20,22,23,32-34,36,44-47,49,58,60-62,64,65,68,88 and 89.

DETAILED ACTION

1. This action is in response to the amendment filed July 21, 2010. This action is made FINAL.

2. Claims 1-2, 4, 10-14, 16, 18-20, 22-23, 32-34, 36, 44-47, 49, 58, 60-62, 64-65, 68, and 88-89 are currently pending.

Claims 36, 49, 58, 60-62, 64-65, 68 have been amended.

Claims 88 and 89 are newly presented.

Claims 1-2, 4, 10-14, 16, 18-20, 22-23, 32-34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on December 15, 2009.

Claims 36, 44-47, 49, 58, 60-62, 64-65, 68, 88-89 are under examination.

Additionally it is noted that Applicants have elected the following species for initial examination:

A. the Protein C sequence (SEQ ID NO: 1)

B. the SNP at position 4732 of the Protein C sequence (SEQ ID NO: 1)

C. systemic inflammatory response syndrome (SIRS) as the disease

D. activated protein C as the anti-inflammatory agent

Prior to allowance of the claim, any non-elected subject matter that is not rejoined with any allowed elected subject matter will be required to be removed from the claims.

Withdrawn Objections

3. The objection made to the Oath/Declaration in section 3 of the Office Action of January 21, 2010 is withdrawn in view of the new Oath/Declaration that has been filed.

The objection made to the specification for containing an embedded hyperlink and/or other form of browser-executable code in section 4 of the Office Action of January 21, 2010 is withdrawn in view of the amendments to the specification.

Withdrawn Rejections

4. The rejection made under 35 USC 112 1st paragraph (written description) in section 2 of the Office Action of January 21, 2010 is withdrawn in view of amendments made to the claims.

The rejection made under 35 USC 102 in section 10 of the Office Action of January 21, 2010 is withdrawn in view of amendments made to the claims.

The rejections made under 35 USC 102 in sections 12-14 of the Office Action of January 21, 2010 are withdrawn in view of amendments made to the claims.

Maintained Objection

Objections to the Specification

5. The specification is objected to because all continuing data must be listed in the first paragraph of the specification if no Application Data Sheet has been filed.

Maintained Rejection

Claim Rejections - 35 USC § 112 1st paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 36, 44-47, 49, 58, 60-62, 64-65, 68, 88-89 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for:

A method of treating SIRS in a human subject, the method comprising selecting a subject that is homozygous for the C allele or heterozygous for the C/T alleles at position 4732 of SEQ ID NO: 1 and administering to said subject activated protein C.

does not reasonably provide enablement for: (i) a method of treating an inflammatory condition in a human subject in need thereof, the method comprising: (a) selecting a human subject having a risk genotype for said inflammatory condition in his protein C sequence wherein the risk genotype is located at a polymorphic site at position 4732 of SEQ ID NO: 1 and (b) administering to said subject selected in (a) activated protein C, wherein the inflammatory condition is SIRS or (ii) a method of administering activated protein C to a selected human subject comprising: administering activated protein C to a

subject with a risk genotype who is selected for said administration on the basis of a protein C which is characterized by a polymorphic site at position 4732 of SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 36, 44-47, 49, 58, 60-62, 64-65, 68, and 88 are broadly drawn to a method of treating an inflammatory condition in a human subject in need thereof. The claims comprise (a) selecting a human subject having a risk genotype for said inflammatory condition in his protein C sequence wherein the risk genotype is located a position 4732 of SEQ ID NO: 1 and administering to said subject selected in (a) activated protein C, wherein the inflammatory condition is SIRS.

Claim 89 is broadly drawn to a method of administering activated protein C to a selected human subject comprising: administering activated protein C to a subject with a risk genotype who is selected for said administration on the basis of a protein C which is characterized by a polymorphic site at position 4732 of SEQ ID NO: 1.

The specification (page 34) defines a risk genotype as an allelic variant (genotype) at one or more polymorphic sites within the Protein C sequence that is indicative of a decreased likelihood of recovery from an inflammatory condition or an increased risk of having a poor outcome. As such the claims encompass selecting a subject having polymorphic variant in the protein C gene that is associated a decreased likelihood of recovery from an inflammatory condition or an increased risk of having a poor outcome.

Claims 36 and 89 only define the polymorphic variant in terms of the position at which it occurs within SEQ ID NO: 1. Therefore the claims broadly encompass detecting any allele (A, T, C or G) at position 4732 of SEQ ID NO: 1. Only claims 58 and 62 recite specific alleles at position 4732 of SEQ ID NO: 1. Claim 58 states that the risk genotype is 4732C. Claim 62 states that the genotype for a decreased risk is 4732 T. Here it is important to note that the claims do not establish whether these alleles need to be in homozygous or heterozygous form to be associated with the risk.

The nature of the claims requires a reliable association between the identity of the nucleotides present at position 4732 of SEQ ID NO: 1 and a decreased likelihood of recovery from SIRs or an increased risk of having a poor outcome.

Example 2 in the specification teaches an association between the C allele at position 4732 of SEQ ID NO: 1 and altered survival and organ dysfunction in critically ill adults with SIRS. Specifically the specification teaches that in human subjects with SIRS, the C allele at position 4732 of SEQ ID NO: 1 (in heterozygous or homozygous form) is correlated with decreased survival and increased multiple organ dysfunction.

Example 4 in the specification is directed to whether or not treatment with activated protein C (XIGRIS) can reduce organ dysfunction in subjects who have sepsis and who have an at risk genotype of protein C such as the C allele at position 4732. The 28 day survival rates for patients who were protein C 4732 CC/CT were compared to patients who were protein C 4732 TT with and without treatment of XIGRIS. The results indicated that XIGRIS treatment increases survival (compared to no treatment) of patients who were protein C 4732 CT/CC (See Fig 7). Further the results indicated

that XIGRIS treatment had virtually no effect on survival rate over 28 days in patients who were protein C 47322 TT.

Accordingly the specification is enabled for a method of treating SIRS in a human subject, the method comprising selecting a subject that is homozygous for the C allele or heterozygous for the C/T alleles at position 4732 of SEQ ID NO: 1 and administering to said subject activated protein C.

The specification does not provide enablement for the claims as broadly written. For example all of the findings in the specification are limited to patients with SIRS yet the claims encompass other types of inflammatory conditions i.e., sepsis and septic shock. Further the claims encompass human and non human subjects but the teachings in the specification are limited to humans. Finally the specification only teaches that in human subjects with SIRS, the C allele at position 4732 of SEQ ID NO: 1 (in heterozygous or homozygous form) is correlated with decreased survival and increased multiple organ dysfunction. However the claims encompass detecting any allele (A, T, C or G) at position 4732 of SEQ ID NO: 1. The claims do not set forth which allele is associated with risk and whether or not the allele needs to be in homozygous or heterozygous form to be associated with the risk.

While the state of the art and level of skill in the art with regard to detection of a polymorphism in a known gene sequence is high, the level of unpredictability in associating any particular polymorphism with a phenotype is even higher. For example it is unpredictable as to whether the results obtained with SIRS can be extrapolated to other inflammatory conditions. The genus of inflammatory conditions is quite large and

each condition has its own pathology and etiology. Again it is noted that the teachings in the specification are limited to an association between the T4732C mutation and altered survival and organ dysfunction in patients with SIRS. Given the differences in the causes and effect of each type of inflammatory disease, one can not extrapolate the results found in SIRS subjects to any type of inflammatory condition.

The specification teaches 2 variants in the protein C gene, namely at positions 4732 and 4800 of SEQ ID NO: 1, which are associated with altered survival and organ dysfunction in critically ill adults with SIRS. To determine if this variant is also associated with altered survival and organ dysfunction in critically ill adults with other types of inflammatory disease such as sepsis or septic shock would require extensive experimentation. Even if the extensive experimentation was performed, there is no assurance that an association would be found. If an association was found then even more experimentation would be required to determine if individuals with sepsis and septic shock also showed an improved response to therapy with activated protein C. Such random, trial by error experimentation is considered to be undue and highly unpredictable. The specification has provided only an invitation to experiment.

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the lack of guidance by the applicant and the particular examples, it is the conclusion that an undue amount of experimentation would be required to make and use the claimed invention in the full scope of the claims.

Response to the Arguments

8. In the response filed July 21, 2010 the Applicants state that they have submitted an ADS to overcome the objection made to the specification. However the ADS has not actually been filed. Therefore the objection is maintained.

Additionally the Applicants traversed the enablement rejection.

Regarding the inflammatory conditions the response asserts that the specification provides enabling support for sepsis, septic shock, or SIRS. The response asserts that the definition of SIRS includes both sepsis and septic shock. This argument has been fully considered but is not persuasive. In the instant case the specification states that SIRS can include sepsis and septic shock however the specification states that sepsis and septic shock are distinctly different from SIRS. For example sepsis is distinct from SIRS because it is defined as at least two SIRS criteria and known or suspected source of infection. Further septic shock is distinct from SIRS because it is defined as sepsis plus at least one organ failure. A SIRS diagnosis does not require a known or suspected source of infection or an organ failure. Based on the definitions in the specification it appears that every person with sepsis and septic shock will also have SIRS but not everyone with SIRS will have sepsis or septic shock. As stated above all of the findings in the specification are limited to patients with SIRS. Therefore the claims are not enabled for sepsis or septic shock.

Regarding the SNP positions the Applicants state that the broadest claims are not being limited to the SNP at position 4732 because the specification adequately supports the SNPs associated with positions 4054 (SEQ ID NO: 2) and 2418 (SEQ ID

NO: 1). The response further discusses linkage disequilibrium. These arguments have been fully considered. Applicants are reminded of their election of the SNP at position 4732 of the Protein C sequence (SEQ ID NO: 1) in response to the election of species requirement. Therefore the claims are only being examined with respect to the SNP at position 4732 of SEQ ID NO: 1. Linkage disequilibrium was only brought up in the previous rejection because claim 36 generically used recite a step of selecting a subject having a risk genotype in their protein C sequence. Therefore claim 36 used to encompass selecting a subject having any polymorphic variant in the protein C gene. As amended claim 36 is now limited to specific polymorphisms. If the additional SNPs recited in claim 36 are ever rejoined with the SNP at position 4732 of SEQ ID NO: 1 then linkage disequilibrium maybe come an issue with respect to enablement.

Finally regarding newly presented claim 89 it is noted that this claim has been included in the enablement rejection because the claim encompasses administering activated protein C to a subject with a risk genotype wherein the risk genotype can be any allele (A, T, C or G) at position 4732 of SEQ ID NO: 1. Further the claim does not establish whether these allele at position 4732 of SEQ ID NO: 1 has to be in homozygous or heterozygous form to be associated with the risk. The claim does not even state what the subject is at risk of. In the instant case the specification only teaches that in human subjects with SIRS, the C allele at position 4732 of SEQ ID NO: 1 (in heterozygous or homozygous form) is correlated with decreased survival and increased multiple organ dysfunction. However the claims are much broader.

Conclusion

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached at 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free).

/Amanda M. Shaw/
Examiner
Art Unit 1634

/Stephen Kapushoc/
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